



# Efficacy and side effect of ritodrine and magnesium sulfate in threatened preterm labor

Min Kyoung Kim<sup>1</sup>, Seung Mi Lee<sup>1</sup>, Jung Won Oh<sup>1</sup>, So Yeon Kim<sup>1</sup>, Hye Gyeong Jeong<sup>1</sup>, Sun Min Kim<sup>2</sup>, Chan Wook Park<sup>1</sup>, Jong Kwan Jun<sup>1</sup>, Seo-kyung Hahn<sup>3</sup>, Joong Shin Park<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Seoul National University College of Medicine; <sup>2</sup>Seoul Metropolitan Government-Seoul National University Boramae Medical Center; <sup>3</sup>Medical Statistics Lab, Department of Medicine, Seoul National University Hospital, Seoul, Korea

## Objective

In terms of efficacy, several previous studies have shown that the success rate in inhibiting preterm labor was not different between magnesium sulfate and ritodrine. However, there is a paucity of information regarding the efficacy of both medications after consideration of intra-amniotic infection, which is one of the most important prognostic factors in patients of threatened preterm birth. The objective of this study was to compare the efficacy and safety of magnesium sulfate with that of ritodrine in preterm labor.

## Methods

In this retrospective cohort study, we included patients who were admitted and treated with either ritodrine or magnesium sulfate with the diagnosis of preterm labor at 24–33.6 weeks of gestational age between January 2005 to April 2015. Patients were divided into 2 groups according to the first-used tocolytics (ritodrine group and magnesium sulfate group). We compared the efficacy and prevalence of side effect in each group. The efficacy of both tocolytics was evaluated in terms of preterm delivery within 48 hours, 7 days, or 37 weeks of gestation and need for 2nd line therapy.

## Results

A total number of 201 patients were enrolled including 177 cases in ritodrine group and 24 cases in magnesium sulfate group. The efficacy of both tocolytics (preterm delivery within 48 hours, 7 days, or 37 weeks of gestation and need for 2nd line therapy) was not different between the 2 groups of cases. In multivariate analysis, gestational age at treatment, twin gestation, intra-amniotic infection and maternal C-reactive protein (CRP) was associated with treatment failure (preterm delivery within 48 hours), but the type of tocolytics was not significantly associated with treatment failure. The type of side effect was different in the 2 groups, but the frequency of total adverse effect, need for discontinuation of therapy because of maternal adverse effect, and severe adverse effect were not different between the two groups of cases.

## Conclusion

The efficacy and safety of magnesium sulfate was similar to ritodrine, and can be a substitute tocolytics. Additionally, failure of tocolytic therapy was determined by gestational age at treatment, twin gestation, intra-amniotic infection, and maternal CRP, not by the type of tocolytics.

**Keywords:** Preterm labor; Ritodrine; Magnesium sulfate; Tocolytics

## Introduction

Considering the effects on perinatal morbidity and mortality, preterm labor is one of the most important problems in obstetrics, accounting for more than one-third of all preterm births [1,2]. So far, ritodrine and magnesium sulfate are the most commonly used tocolytics for preterm labor. Ritodrine is an approved drug by Korean Food and Drug Administration and is the most commonly used medication as a tocolytics. However, side effects such as palpitations, pulmonary edema,

Received: 2017.04.24. Revised: 2017.07.27. Accepted: 2017.07.27.

Corresponding author: Joong Shin Park

Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea

E-mail: jsparkmd@snu.ac.kr

<http://orcid.org/0000-0002-5246-0477>

Articles published in *Obstet Gynecol Sci* are open-access, distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2018 Korean Society of Obstetrics and Gynecology

hands tremors, hypokalemia, and hyperglycemia are known to occur [3,4]. The Magnesium sulfate is not approved for tocolytics and is used as an off-label drug for a preterm labor, in addition to other purposes such as prevention of eclampsia and prevention of cerebral palsy in premature infants [5]. Magnesium sulfate may also cause side effects such as nausea and vomiting, lethargy, dyspnea, headache, hypotension, and dizziness [1,5,6]. Therefore, it may be needed to evaluate the safety of magnesium sulfate in comparison with ritodrine.

In terms of efficacy to inhibit uterine contractions, several previous studies have shown that the success rate in inhibiting preterm labor (within 48 hours or within 7 days) was not different between magnesium sulfate and ritodrine [2,7,8]. However, there is a paucity of information regarding the efficacy of both medications after consideration of intra-amniotic infection, although numerous data suggest that intra-amniotic infection is one of the most important prognostic factors in patients of threatened preterm birth [9-11].

The objective of this study was to compare the efficacy and safety of magnesium sulfate with that of ritodrine in preterm labor, and to analyze the factors affecting the efficacy of the drug in patients for the treatment of preterm labor.

## Materials and Methods

### 1. Study population

In this retrospective study, pregnant women who were treated with tocolytics (ritodrine or magnesium sulfate) with the diagnosis of preterm labor (24–33.6 weeks of gestation) and underwent amniocentesis to evaluate the presence of infection in the amniotic fluid or fetal lung maturation in Seoul National University Hospital were included between January 2005 and April 2015. Women diagnosed with premature rupture of membrane or pre-eclampsia were excluded. The study population was divided into ritodrine group and magnesium sulfate group according to the type of first-line tocolytics.

### 2. Definition

Preterm labor was defined as regular uterine contractions, and the choice of first tocolytics drug and the administration dosage of tocolytics was at the discretion of attending physician. Usually ritodrine was administered with an initial dose of 6.4 mg/hr with increment of 3.2 mg/hr every 15 minutes until the cessation of uterine contractions, and magnesium sulfate

was given as a 0.004–0.006 g loading dose followed 1.2–3 g/hr of maintenance dose.

The efficacy of tocolytics was assessed in terms of inhibition of preterm birth within 48 hours, within 7 days, or within 37 weeks of gestation, and the frequency of changing to the second-line therapy was also evaluated. To compare the efficacy of both medications with consideration of other clinical factors, the patients were divided into treatment success group and failure group according to whether they were delivered within 48 hours or not. The gestational age of initiation of tocolytics administration, the gestational age of delivery, the frequency of second-line therapy needed, the duration of medication, the rate of twin pregnancy, maternal age, parity, the presence or absence of amniotic fluid infection, and maternal C-reactive protein (CRP) were compared between 2 groups of cases.

The side effects of the drugs were analyzed in women who used only one tocolytics, and women who needed second-line therapy were excluded from the analysis of side effects. In terms of adverse events, the tachycardia was defined as heart rate exceeding 110 rate/min, the tachypnea was defined as respiration rate exceeding 20 times/min, and the hypokalemia was defined as a plasma potassium level of less than 3.0 mEq/L. Hyperglycemia was defined as the state of above 200 mg/dL blood sugar level regardless of diet. Amniotic fluid infection was defined as a positive result in amniotic fluid culture.

### 3. Statistical analysis

Statistical analysis was performed using SPSS 23.0 for windows (IBM Corp., Armonk, NY, USA). Mann-Whitney *U* test was used to examine the differences between the 2 groups in terms of the continuous variables. The  $\chi^2$  test was used to compare proportions. Multivariate logistic regression was done for analysis risk factors for treatment failure on the basis of significant factor affecting efficacy of tocolytics. *P*-value <0.05 was considered statistically significant.

## Results

### 1. Clinical characteristics

A total of 201 pregnant women were analyzed. Among them, 177 patients (88.1%) were treated with ritodrine and 24 patients (11.9%) were treated with magnesium sulfate. Magnesium sulfate was considered as a first-line therapy

especially for patients whose underlying status was hyperthyroidism, cardiac disease or diabetes. Table 1 shows the patient characteristics of study population. There was no significant difference in the maternal age, gestational week at treatment, maternal CRP, and proportion of twin pregnancy, steroid use, positive amniotic fluid culture between the 2 groups of cases. However, there was a difference in parity between the 2 groups ( $P=0.020$ ).

## 2. Efficacy evaluation between ritodrine and magnesium sulfate

Table 2 shows the efficacy of both tocolytics. Gestational age at delivery, median duration of therapy, preterm delivery within 48 hours, 7 days, or 37 weeks, and the need for 2nd line therapy were not significantly different between the two groups of cases though the rate of delivery after 37 weeks (ritodrine group=14.8% and magnesium sulfate group=4.2%) was lower and need for 2nd line therapy (ritodrine group=7.3% and magnesium sulfate group=12.5%) was higher in magnesium sulfate group.

To evaluate clinical factors which determine preterm delivery within 48 hours of treatment, study population was divided into 2 groups according to the occurrence of preterm delivery within 48 hours of treatment; treatment success group (patients who delivered after 48 hours of treatment) and treatment failure group (patients who delivered preterm within 48 hours of treatment). The type of tocolytics was not significantly associated with treatment failure. In addition, there was no significant difference in the maternal age, parity, and steroid use between treatment success group and treatment failure group (Table 3). However, patients in treatment failure group had higher gestational age at treatment and maternal CRP, and higher proportion of twin pregnancy and positive amniotic fluid culture than those in treatment success group.

In multivariate analysis, type of first-line tocolytics was not associated with treatment failure even after adjustment for confounding factors. In the multivariate logistic regression model, gestational age of tocolytics administered, twin pregnancy, positive amniotic fluid culture, and maternal CRP were significant risk factors for treatment failure (Table 4).

**Table 1.** Patient characteristics

Characteristics	Ritodrine (n=177)	Magnesium sulfate (n=24)	P-value
Maternal age	31.6 (21–57)	31.7 (19–40)	0.699
Nulliparity	125 (70.6)	11 (45.8)	0.020
Twin pregnancy	65 (36.7)	8 (33.3)	0.824
Corticosteroid	148 (84.1)	20 (83.3)	1.000
Positive amniotic fluid culture	12 (7.0)	2 (8.7)	0.673
Maternal CRP	0.45 (0.01–13.14)	0.46 (0.01–7.80)	0.825
Gestational age at treatment	29.3 (24.0–34.0)	29.2 (25.0–34.0)	0.195

Values are expressed as median and range or number of subjects (%).  
CRP, C-reactive protein.

**Table 2.** Efficacy of ritodrine and magnesium sulfate

Variables	Ritodrine (n=177)	Magnesium sulfate (n=24)	P-value
Gestational age at delivery	33.3 (24.0–40.1)	32.5 (26.6–38.1)	0.862
Median duration of therapy (day)	5 (1–79)	3 (1–43)	0.364
Median duration of therapy in patients with delivery delayed 7 day or more	17 (7–60)	13 (7–27)	0.287
Delivery delayed 48 hr	141 (79.6)	17 (81.0)	1.000
Delayed 7 day	75 (42.4)	10 (41.7)	1.000
After 37 wk	26 (14.8)	1 (4.2)	0.211
2nd line therapy needed	13 (7.3)	3 (12.5)	0.414

Values are expressed as median and range.

**Table 3.** Characteristic difference according to the efficacy of tocolytics

Variables	Treatment success group (delivery after 48 hr of treatment, n=163)	Treatment failure group (delivery within 48 hr of treatment, n=28)	P-value
Maternal age	31.6 (19–57)	32.3 (24–41)	0.366
Nulliparity	112 (68.7)	17 (63.0)	0.657
Twin pregnancy	56 (34.4)	16 (57.1)	0.033
Corticosteroid	135 (83.3)	23 (85.2)	1.000
Positive amniotic fluid culture	9 (5.7)	5 (19.2)	0.031
Maternal CRP	0.43 (0.01–7.60)	1.54 (0.01–14.13)	0.000
Gestational age at treatment	28.5 (24.1–34.0)	31.2 (24.0–34.0)	0.029
Type of first line tocolytics			0.167
Ritodrine	135 (82.8)	21 (75.0)	
Magnesium sulfate	14 (8.5)	5 (17.9)	
Used tocolytics			0.119
Ritodrine	135 (82.8)	21 (75.0)	
Ritodrine → 2nd line	11 (6.7)	2 (7.1)	
Magnesium sulfate	14 (8.5)	5 (17.9)	
Magnesium sulfate → 2nd line	3 (1.9)	0 (0.0)	

Values are expressed as median and range or number of subjects (%).  
CRP, C-reactive protein.

**Table 4.** The relationship between various clinical factors and tocolytics treatment failure, analyzed by multiple logistic regression analysis

Variables	Adjusted OR	95% CI	P-value
Used tocolytics (magnesium sulfate)	1.186	0.286–4.917	0.814
Gestational age at treatment	1.197	1.013–1.414	0.035
Twin pregnancy	3.503	1.280–9.587	0.015
Positive amniotic fluid culture	6.041	1.484–24.583	0.012
Maternal CRP	1.539	1.207–1.962	0.001

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

In study population, 14 patients (7%) showed positive amniotic fluid culture result. The culture microorganisms were *Ureaplasma* (8 cases), *Mycoplasma*, *Escherichia coli*, *Candida*, *Gardnerella*, and *Streptococcus* (polymicrobial invasion was present in 3 cases). Table 5 compares the clinical characteristics and pregnancy outcomes according to the result of amniotic fluid culture. Patients with positive amniotic fluid culture had higher maternal CRP levels and had higher risk of preterm delivery (within 48 hours and with 7 days) than those with negative amniotic fluid culture.

### 3. Maternal side effects

Patients who needed both ritodrine and magnesium sulfate for tocolysis as first line and second line therapy were ex-

cluded from the analysis of side effects. The side effect of the first-line therapy was compared between the ritodrine group of 164 patients and magnesium sulfate group of 21 patients. In the group using ritodrine, several side effects were occurred in the order of palpitations (81.7%), hand tremor (57.9%), tachycardia (47.0%), chest discomfort (34.1%), tachypnea (20.7%), and nausea (14.6%). In the magnesium sulfate group, the common side effects were burning sensation (76.2%), lethargy (66.7%), dizziness (47.6%), and nausea (19.0%). When ritodrine was used, side effects such as palpitations, hand tremor, tachycardia, chest discomfort, and tachypnea were significantly more frequent, and when magnesium sulfate was used, facial flushing, lethargy and dizziness were more significantly increased than in ritodrine group

(Table 6). The probability of occurrence of one or more side effects was 93.9% for ritodrine group and 90.5% for magnesium sulfate group ( $P=0.630$ ).

In terms of severe side effects, the first-line tocolytic treatment was discontinued in seven patients (4.2%) in ritodrine group and two patients (9.5%) in magnesium sulfate group

**Table 5.** Clinical characteristics and pregnancy outcomes according to the result of amniotic fluid culture

Characteristics	Positive amniotic fluid culture (n=14)	Negative amniotic fluid culture (n=187)	P-value
Maternal age	33.5 (26–41)	31.0 (19–43)	0.768
Nulliparity	6 (42.9)	58 (32.0)	0.290
Twin pregnancy	6 (42.9)	74 (41.1)	0.555
Corticosteroid	13 (92.9)	152 (84.4)	0.349
Maternal CRP	1.78 (0.00–14.13)	0.36 (0.00–10.37)	0.024
Gestational age at treatment	28.0 (24.0–33.0)	29.2 (20.6–34.0)	0.158
Gestational age at delivery	28.3 (24.0–33.1)	33.0 (24.3–40.1)	0.250
Delivery delayed 48 hr	9 (64.3)	149 (87.1)	0.036
Delayed 7 day	2 (14.3)	83 (44.4)	0.028
After 37 wk	0 (0.0)	27 (15.0)	0.113
Type of first line tocolytics			
Ritodrine	12 (85.7)	160 (88.4)	0.511
Magnesium sulfate	2 (14.3)	21 (11.6)	0.511
2nd line therapy needed	0 (0.0)	16 (8.8)	0.289

Values are expressed as median and range or number of subjects (%).  
CRP, C-reactive protein.

**Table 6.** Type of side effect of ritodrine and magnesium sulfate

Side effects	Ritodrine (n=164)	Magnesium sulfate (n=21)	P-value
Tachycardia	77 (47.0)	0 (0.0)	0.000
Tachypnea	34 (20.7)	0 (0.0)	0.011
Hypokalemia	4 (2.4)	0 (0.0)	0.615
Hyperglycemia	0 (0.0)	0 (0.0)	-
Palpitation	134 (81.7)	0 (0.0)	0.000
Tremor	95 (57.9)	0 (0.0)	0.000
Chest pain	2 (1.2)	0 (0.0)	0.785
Chest discomfort	56 (34.1)	2 (9.5)	0.015
Nausea	24 (14.6)	4 (19.0)	0.396
Vomiting	7 (4.2)	1 (4.7)	1.000
Dizziness	12 (7.3)	101 (47.6)	0.000
Hot flush	22 (13.4)	16 (76.2)	0.000
Lethargy	8 (4.9)	14 (66.7)	0.000
Pulmonary edema	5 (3.0)	0 (0.0)	0.544
Respiratory rate <8/min	0 (0.0)	0 (0.0)	-
Urine output <100 cc/4 hr	0 (0.0)	0 (0.0)	-
Hypotension (dBP <40 mmHg)	0 (0.0)	0 (0.0)	-
Total adverse event	154 (93.9)	19 (90.5)	0.630

Values are expressed as number of subjects (%).

**Table 7.** Severe side effect of ritodrine and magnesium sulfate

Severe side effects	Ritodrine (n=164)	Magnesium sulfate (n=21)	P-value
Maternal death	0 (0.0)	0 (0.0)	-
Cardiac arrest	0 (0.0)	0 (0.0)	-
Respiratory arrest	0 (0.0)	0 (0.0)	-
Admission to ICU	0 (0.0)	0 (0.0)	-
Discontinuation of therapy because of maternal adverse outcome	7 (4.2)	2 (9.5)	0.271

Values are expressed as number of subjects (%).

ICU, intensive care unit.

because of intolerable side effects of the drug ( $P=0.271$ , Table 7). The causes of discontinuation of the treatment in the ritodrine group were chest discomfort (3 cases), palpitation (3 cases) and pulmonary edema (1 case). In the magnesium sulfate group, the causes of discontinuation of the treatment were lethargy which may make it difficult to open the eyes (1 case) and chest discomfort (1 case). The longer duration of tocolytics treatment (for more than 48 hours) was not associated with the discontinuation of therapy because of maternal adverse outcome (3.3% in patients who were treated with tocolytics for more than 48 hours vs. 7.1% in patients who were not).

No severe maternal complications such as maternal death, cardiac arrest, respiratory arrest, and intensive care unit admission were occurred in both groups.

## Discussion

The principal finding of the current study was; 1) The efficacy (preterm delivery within 48 hours, 7 days, or 37 weeks of gestation and need for 2nd line therapy) was not different between ritodrine and magnesium sulfate; 2) In multivariate analysis, gestational age at treatment, twin gestation, intra-amniotic infection and maternal CRP was associated with treatment failure (preterm delivery within 48 hours), but the type of tocolytics was not significantly associated with treatment failure; 3) The type of side effect was different in the 2 groups, but the frequency of total adverse effect, need for discontinuation of therapy because of maternal adverse effect, and severe adverse effect were not different between the 2 groups of cases.

Until now, several medications have been used in preterm labor, and ritodrine and magnesium sulfate are the most

frequently used tocolytics [4,7,12]. Magnesium sulfate is known to suppress the uterine contraction by antagonism to calcium ions [5]. Ritodrine is a  $\beta$ -adrenergic agonist that binds to  $\beta$ -sympathetic receptors in the uterine smooth muscle cell membrane and relaxes the uterine smooth muscle by decreasing the concentration of calcium that causes muscle contraction [12]. However, the problem with  $\beta$ -adrenergic agonists is that  $\beta$ -sympathetic receptors are distributed not only in the uterine muscle but also in the vascular wall, resulting in unintended side effects. The side effects caused by this include maternal cardiovascular side effects, hypokalemia, and hyperglycemia. The most common side effects of ritodrine administration are tachycardia, hypotension, and chest discomfort, but uncommon fatal side effects such as pulmonary edema and myocardial infarction have been reported [1,3].

In this study, the safety and efficacy of magnesium sulfate, as an alternative tocolytic, was compared with that of ritodrine. As a result of specific mechanism of action of both tocolytics, side effects related with vital signs such as palpitations, hand tremor, tachycardia, chest discomfort, and tachypnea were significantly more frequent in ritodrine group whereas facial flushing, lethargy, and dizziness were much significantly occurred in magnesium sulfate group. The overall side effects showed different frequency of incidence according to each drug use, but there was no difference in severe side effects, in terms of discontinuation of drug use due to severe side effects and the fatal maternal side effects (maternal death, cardiac arrest, respiratory arrest, and intensive care unit admission). Therefore, it can be concluded that ritodrine and magnesium sulfate are similar in terms of safety.

In addition, in order to evaluate the efficacy of the tocolytics, treatment success (delay of delivery within 48 hours after drug administration) was analyzed. The type of first-line tocolytics (ritodrine vs. magnesium sulfate) was not significant

determinant of treatment failure. Therefore, we might conclude that magnesium sulfate as a tocolytics in preterm labor patients is not different from ritodrine in terms of efficacy.

There have been several studies which showed that the efficacy was not different between magnesium sulfate and ritodrine [3,4]. Recently, Hwang et al. [13] reported multicenter study on the practice pattern in management of threatened preterm labor in Korea. In this study, the effectiveness of ritodrine and magnesium sulfate was similar and the poor tolerance to therapy was comparable between the 2 tocolytics, and these results are consistent with the result of the current study. However, the comparison of efficacy after adjustment for intra-amniotic infection has not been well determined, although numerous studies have suggested that intra-amniotic infection is the major risk factor of preterm delivery [9-11]. In the current study, the efficacy of treatment success was not related to the type of first-line tocolytics, but was influenced by the gestational age of tocolytics administered, twin pregnancy, amniotic fluid infection, and maternal CRP.

This study was based on the retrospective study with patients who underwent amniocentesis among the inpatients due to preterm labor. Therefore, the number of magnesium sulfate used group was relatively small, and the decision on type of tocolytics was at the discretion of attending physician which might result in different indications for both tocolytics and in selection bias (for example, magnesium sulfate might be used as a first-line therapy especially for patients with medical disease such as hyperthyroidism, cardiac disease, or diabetes). Further studies through prospective randomization studies may be needed to evaluate the efficacy and safety of magnesium sulfate.

And about magnesium sulfate, there are 2 more important points. Magnesium sulfate has a neuroprotective effect for preterm birth before 32 weeks of gestation. So we should consider magnesium sulfate especially for patients who have high risk for preterm birth within 32 weeks [5]. In addition, the concerns on its adverse effect of fetal bone should be kept in mind in patients who need magnesium sulfate for more than 7 days [14].

In conclusion, the efficacy and safety of magnesium sulfate was similar to ritodrine, and can be a substitute tocolytics. Additionally, failure of tocolytic therapy was determined by gestational age at treatment, twin gestation, intra-amniotic infection and maternal CRP, not by the type of tocolytics.

## Acknowledgements

This research was supported by a grant (14172MFDS178) from Ministry of Food and Drug Safety in 2014.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## Reference

1. Kim JH, Ahn KH, Kim JY, Jeong YJ, Cho SN. A comparison for efficacy and safety of magnesium sulfate (Magrose), ritodrine hydrochloride (Yutopar) and nifedipine (Adalat) in the management of preterm labor. *Korean J Obstet Gynecol* 2001;44:1165-70.
2. Jørgensen JS, Weile LK, Lamont RF. Preterm labor: current tocolytic options for the treatment of preterm labor. *Expert Opin Pharmacother* 2014;15:585-8.
3. Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta-adrenergic agonist ritodrine. *N Engl J Med* 1992;327:308-12.
4. Haram K, Mortensen JH, Morrison JC. Tocolysis for acute preterm labor: does anything work. *J Matern Fetal Neonatal Med* 2015;28:371-8.
5. American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee opinion no. 455: magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol* 2010;115:669-71.
6. Driul L, Londero AP, Adorati-Menegato A, Vogrig E, Bertozzi S, Fachechi G, et al. Therapy side-effects and predictive factors for preterm delivery in patients undergoing tocolysis with atosiban or ritodrine for threatened preterm labour. *J Obstet Gynaecol* 2014;34:684-9.
7. Kam KY, Lamont RF. Developments in the pharmacotherapeutic management of spontaneous preterm labor. *Expert Opin Pharmacother* 2008;9:1153-68.
8. McCubbin K, Moore S, MacDonald R, Vaillancourt C. Medical transfer of patients in preterm labor: treatments and tocolytics. *Prehosp Emerg Care* 2015;19:103-9.
9. Romero R, Dey SK, Fisher SJ. Preterm labor: one syn-

- drome, many causes. *Science* 2014;345:760-5.
10. Watts DH, Krohn MA, Hillier SL, Eschenbach DA. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. *Obstet Gynecol* 1992;79:351-7.
  11. Romero R, Manogue KR, Mitchell MD, Wu YK, Oyarzun E, Hobbins JC, et al. Infection and labor. IV. Cachectin-tumor necrosis factor in the amniotic fluid of women with intraamniotic infection and preterm labor. *Am J Obstet Gynecol* 1989;161:336-41.
  12. van Vliet EO, Boormans EM, de Lange TS, Mol BW, Oudijk MA. Preterm labor: current pharmacotherapy options for tocolysis. *Expert Opin Pharmacother* 2014;15:787-97.
  13. Hwang HS, Na SH, Hur SE, Lee SA, Lee KA, Cho GJ, et al. Practice patterns in the management of threatened preterm labor in Korea: a multicenter retrospective study. *Obstet Gynecol Sci* 2015;58:203-9.
  14. Holcomb WL Jr, Shackelford GD, Petrie RH. Magnesium tocolysis and neonatal bone abnormalities: a controlled study. *Obstet Gynecol* 1991;78:611-4.